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(54) **SILVER NANOPARTICLE ANTIMICROBIAL COATING FOR LONG-TERM AND SHORT-TERM INFECTION RESISTANCE**

(71) Applicant: **PACESETTER, INC.**, Sylmar, CA (US)

(72) Inventors: **Yelena Nabutovsky**, Sunnyvale, CA (US); **Gene A. Bornzin**, Simi Valley, CA (US); **Annapurna Karicherla**, Valencia, CA (US); **Nirav Dalal**, Porter Ranch, CA (US); **Prashant Dinesh**, Bangalore (IN); **Richard Samade**, Northridge, CA (US); **John W. Poore**, South Pasadena, CA (US)

(73) Assignee: **PACESETTER, INC.**, Sylmar, CA (US)

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B82Y 5/00	(2011.01)
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(58) **Field of Classification Search**

CPC B82Y 5/00; B82Y 30/00; B22F 1/0018; B22F 2303/01; C01P 2004/54; A61K 9/1611

See application file for complete search history.

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(57) **ABSTRACT**

Disclosed herein is an implantable medical device including an antimicrobial layer. The antimicrobial layer may include a first distinct size of silver nanoparticles, a second distinct size of silver nanoparticles, and a third distinct size of silver nanoparticles. The antimicrobial layer extends over a surface of the implantable medical device, and, in some instances, the surface of the implantable medical device may serve as a substrate on which the antimicrobial layer is deposited.

9 Claims, 4 Drawing Sheets

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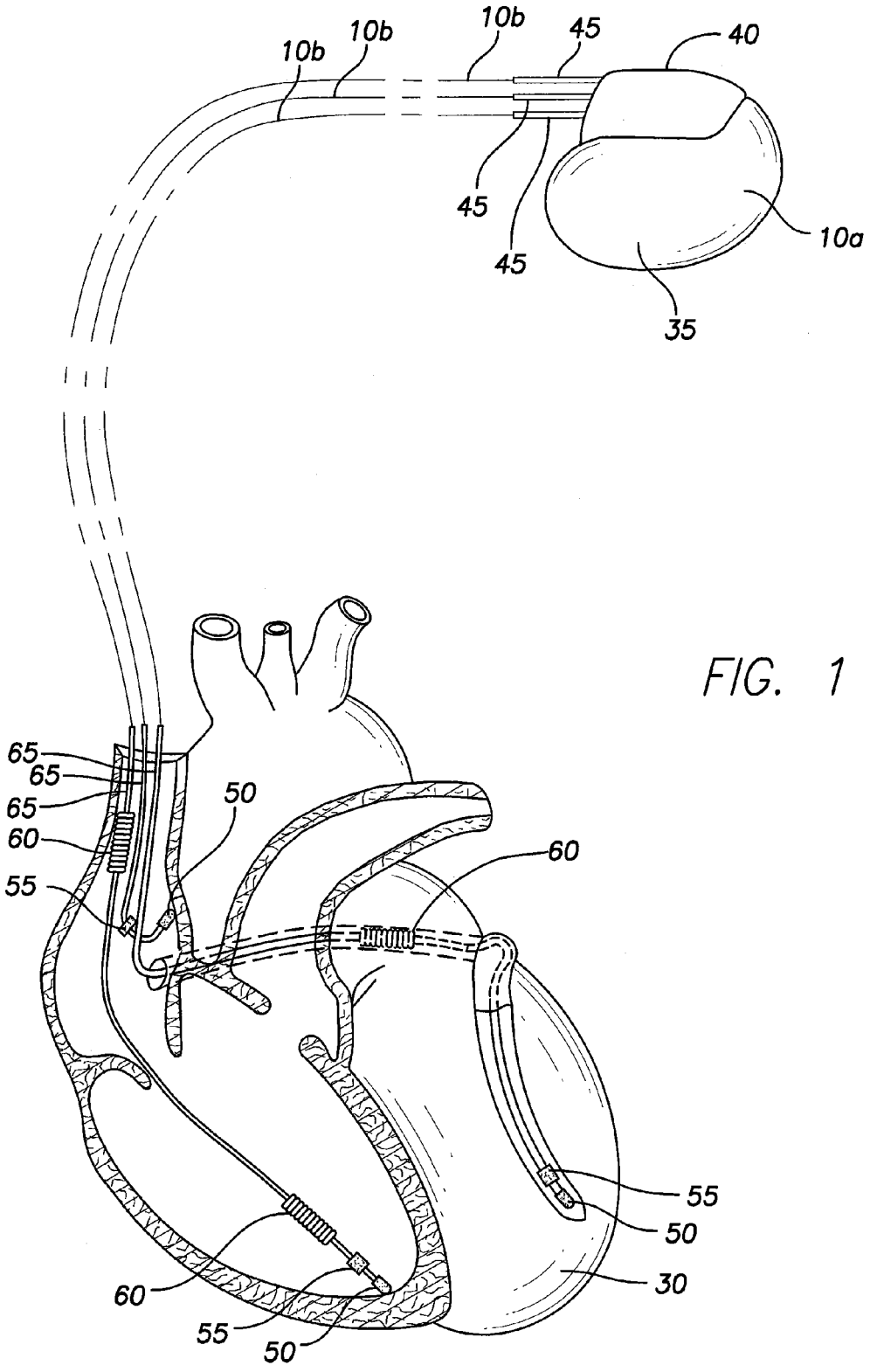

FIG. 1

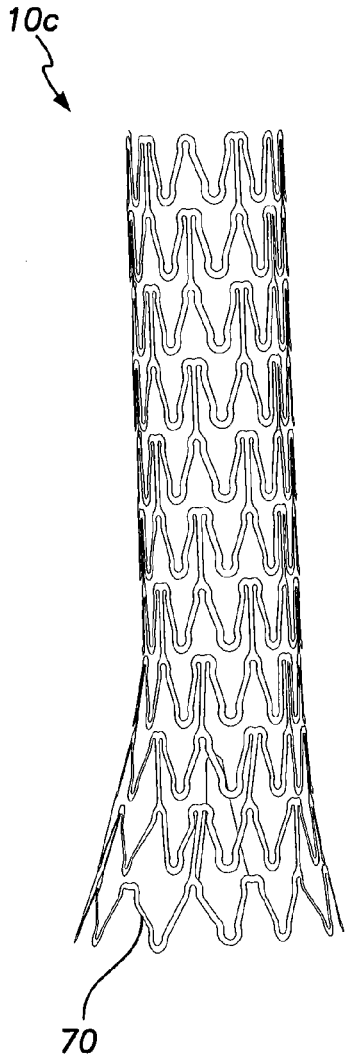

FIG. 2

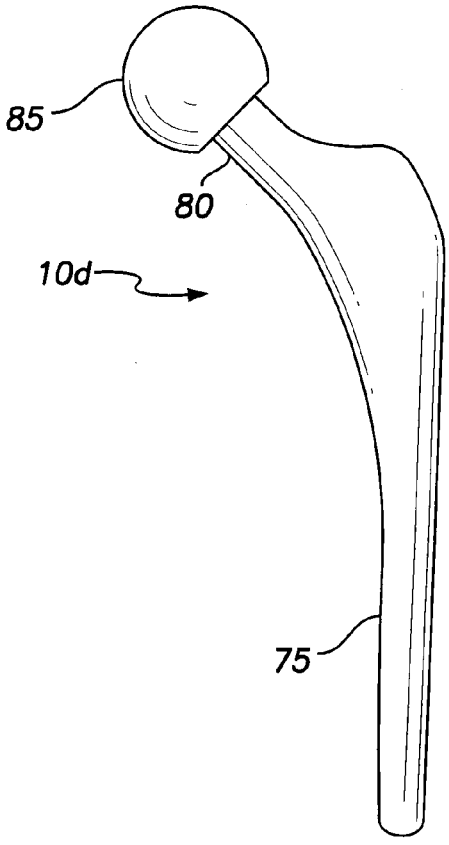

FIG. 3

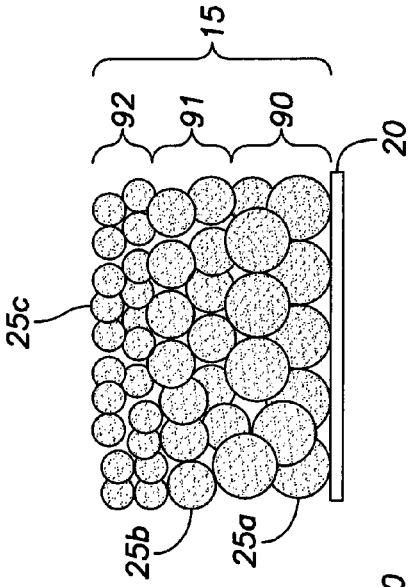

FIG. 4C

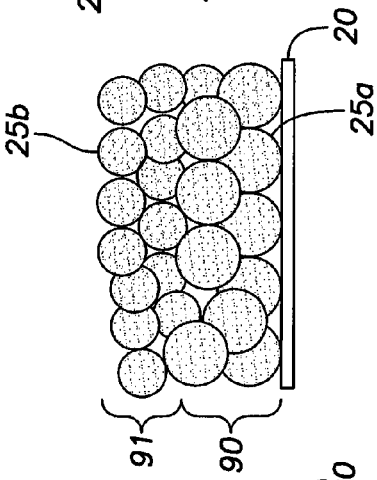

FIG. 4B

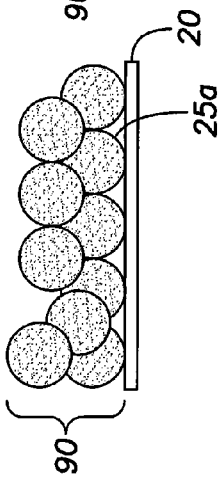

FIG. 4A

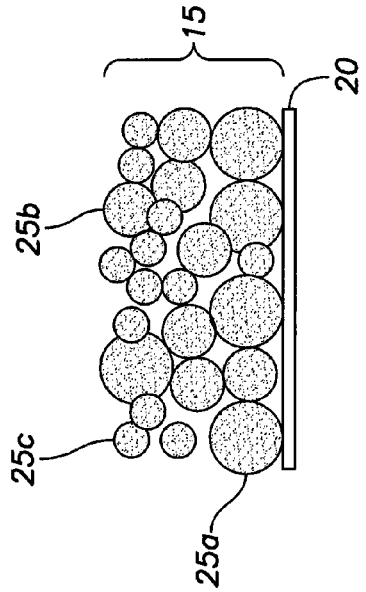

FIG. 5

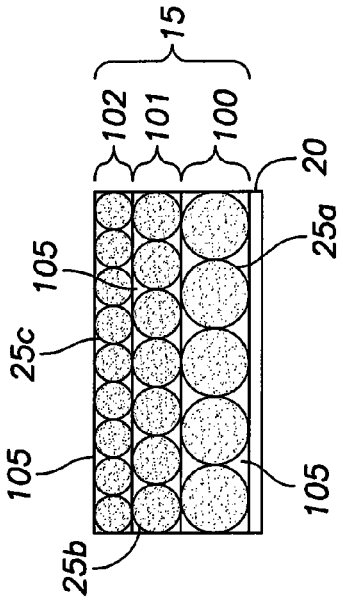

FIG. 6C

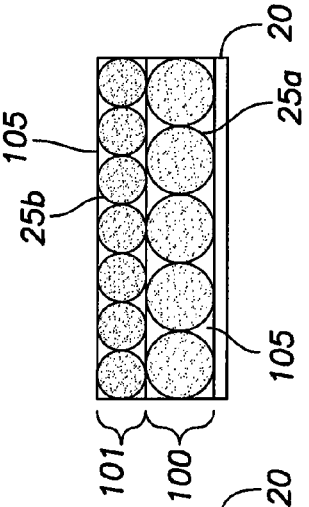

FIG. 6B

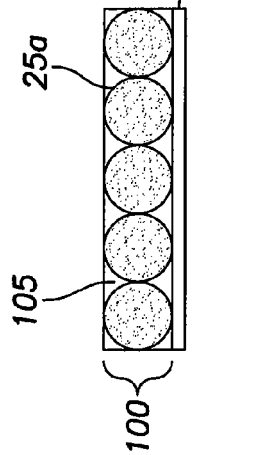

FIG. 6A

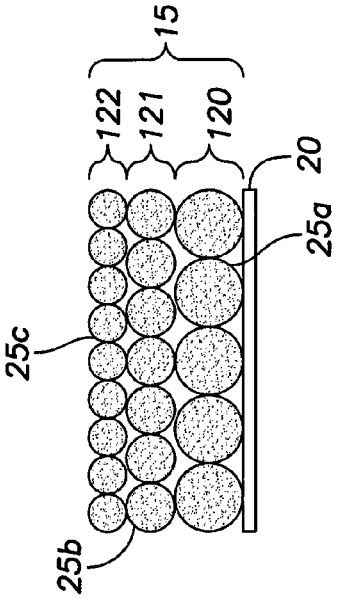

FIG. 7C

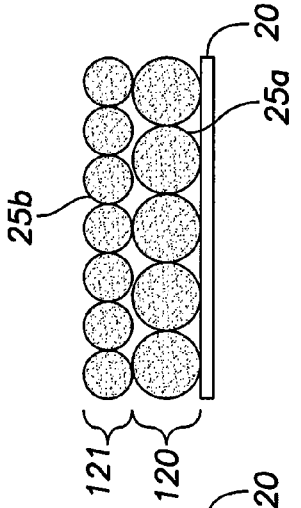

FIG. 7B

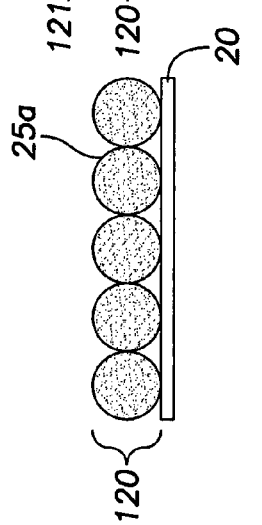

FIG. 7A

SILVER NANOPARTICLE ANTIMICROBIAL COATING FOR LONG-TERM AND SHORT-TERM INFECTION RESISTANCE

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a division of U.S. patent application Ser. No. 13/415,747, filed Mar. 8, 2012.

FIELD OF THE INVENTION

Aspects of the present invention relate to medical apparatus and methods. More specifically, the present invention relates to antimicrobial coatings, methods of depositing such coatings on substrates, and medical devices employing such coatings.

BACKGROUND OF THE INVENTION

Implantable device-related infection (DRI) is a serious problem that arises in about 2% of de novo implants of implantable cardioverter defibrillators (ICDs), and pacemakers. The incidence is higher for patients that are diabetic, on kidney dialysis, receiving device replacements, and undergoing lead revisions. In addition, anecdotal evidence suggests that DRIs are increasing due to growth in device complexity and are more prevalent when implanting physicians are less experienced. Similar DRI rates also occur for other types of medical device implants, including, for example, orthopedic implants, stents, catheters, etc.

A DRI is extremely costly with combined medical and surgical treatment for a DRI ranging from $25,000 to $50,000. Also, a DRI makes the patient susceptible to potentially fatal complications.

The time course of infection development is not fully understood and varies greatly. However, it has been reported that about 30 percent of infections arise less than one month post-implant, another 35 percent occur between one month and twelve months post-implant, and the remainder appear more than a year post-implant.

There is a dearth of technologies available to prevent implantable DRIs. One known product that is commercially available is the AIGIS$_{Rx}$ AntiBacterial Envelope, which is manufactured by TyRx Pharma, Inc. This antimicrobial pouch, designed for use with pacemakers and ICDs, is a polypropylene mesh that is shaped into a pocket and is impregnated with antibiotics. The pacemaker or ICD is placed into the AIGIS$_{Rx}$ and the covered device is subsequently implanted. The antibiotics (minocycline and rifampin) are eluted over a minimum period of 7 days in order to prevent DRIs. There are several shortcomings to this approach. First, the approach requires the implanting physician to execute an extra step of placing the pouch over the device. Second, the pouch adds bulk to the implant, which increases patient discomfort post-surgery. Third, device replacement or explant is more difficult due to growth of tissue into the mesh. Finally, the antibiotics only act for a short period of time and, as a result, do not address long-term DRIs.

There is a need in the art for a solution to both short-term and long-term DR's that overcomes all of the above-mentioned issues.

BRIEF SUMMARY OF THE INVENTION

A first embodiment of the present disclosure may take the form of an implantable medical device including an antimicrobial layer including a first distinct size of silver nanoparticles, a second distinct size of silver nanoparticles, and a third distinct size of silver nanoparticles. The antimicrobial layer extends over a surface of the implantable medical device, and, in some instances, the surface of the implantable medical device may serve as a substrate on which the antimicrobial layer is deposited.

In one version of the first embodiment, the third distinct size of silver nanoparticles includes silver nanoparticles with a diameter of between approximately 1.5 times and approximately 2 times the diameter of the silver nanoparticles of the second distinct size of silver nanoparticles. The second distinct size of silver nanoparticles includes silver nanoparticles with a diameter of approximately 2 times the diameter of the silver nanoparticles of the first distinct size of silver nanoparticles. For example, the first distinct size of silver nanoparticles may include silver nanoparticles with a diameter of approximately 5 nm, the second distinct size of silver nanoparticles may include silver nanoparticles with a diameter of approximately 10 nm, and the third distinct size of silver nanoparticles may include silver nanoparticles with a diameter of between approximately 15 nm and approximately 20 nm.

In one version of the first embodiment, the first distinct size of silver nanoparticles are generally confined in a first sub-layer of the antimicrobial layer, the second distinct size of silver nanoparticles are generally confined in a second sub-layer of the antimicrobial layer, and the third distinct size of silver nanoparticles are generally confined in a third sub-layer of the antimicrobial layer. In versions of the first embodiment where the surface of the implantable medical device acts as a substrate for the antimicrobial layer, the third sub-layer of the antimicrobial layer may adhere directly to the substrate, the first sub-layer may form an exposed outer surface of the antimicrobial layer, and the second sub-layer may be located between the first sub-layer and the third sub-layer.

In one version of the first embodiment, the first sub-layer, second sub-layer, and third sub-layer are the products of a multi-step wet deposition process. In one version of the first embodiment, the first sub-layer, second sub-layer, and third sub-layer are the products of a multi-step PEM process. In one version of the first embodiment, the first sub-layer, second sub-layer, and third sub-layer are the products of a multi-step sintering process.

In one version of the first embodiment, the first distinct size of silver nanoparticles are confined in a polymer material forming at least part of a first sub-layer of the antimicrobial layer, the second distinct size of silver nanoparticles are confined in a polymer material forming at least part of a second sub-layer of the antimicrobial layer, and the third distinct size of silver nanoparticles are confined in a polymer material forming at least part of a third sub-layer of the antimicrobial layer. The first sub-layer, second sub-layer, and third sub-layer are the products of a multi-step polymer deposition process.

In one version of the first embodiment, the device is at least one of an implantable pulse generator or an implantable medical lead. In another version of the first embodiment, the device is at least one of an implantable medical stent or an implantable arthroplasty implant.

A second embodiment of the present disclosure may take the form of a method of applying antimicrobial protection to an implantable medical device. In one version of the second embodiment, the method includes applying an antimicrobial layer to a surface of the implantable medical device, the antimicrobial layer including multiple distinct sizes of silver nanoparticles.

In one version of the second embodiment, the multiple distinct sizes of silver nanoparticles includes a first, second and third distinct sizes of silver nanoparticles. The third distinct size of silver nanoparticles may include silver nanoparticles with a diameter of between approximately 1.5 times and approximately 2 times the diameter of the silver nanoparticles of the second distinct size of silver nanoparticles. The second distinct size of silver nanoparticles may include silver nanoparticles with a diameter of approximately 2 times the diameter of the silver nanoparticles of the first distinct size of silver nanoparticles. For example, the first distinct size of silver nanoparticles may include silver nanoparticles with a diameter of approximately 5 nm, the second distinct size of silver nanoparticles may include silver nanoparticles with a diameter of approximately 10 nm, and the third distinct size of silver nanoparticles may include silver nanoparticles with a diameter of between approximately 15 nm and approximately 20 nm.

In one version of the second embodiment, the method further includes causing the first distinct size of silver nanoparticles to be generally confined in a first sub-layer of the antimicrobial layer, the second distinct size of silver nanoparticles to be generally confined in a second sub-layer of the antimicrobial layer, and the third distinct size of silver nanoparticles to be generally confined in a third sub-layer of the antimicrobial layer. The surface of the implantable medical device may act as a substrate for the antimicrobial layer. Accordingly, the method may further include applying the third sub-layer of the antimicrobial layer so as to adhere directly to the substrate, applying the first sub-layer to as to form an exposed outer surface of the antimicrobial layer, and applying the second sub-layer so as to be located between the first sub-layer and the third sub-layer. The sub-layers may be applied via a multi-step wet deposition process or via a multi-step PEM process.

In another version of the second embodiment, the method may further include causing the first distinct size of silver nanoparticles to be confined in a polymer material forming at least part of a first sub-layer of the antimicrobial layer, causing the second distinct size of silver nanoparticles to be confined in a polymer material forming at least part of a second sub-layer of the antimicrobial layer, and causing the third distinct size of silver nanoparticles to be confined in a polymer material forming at least part of a third sub-layer of the antimicrobial layer. Such sub-layers may be applied via a multi-step polymer deposition process or a multi-step sintering process.

While multiple embodiments are disclosed, still other embodiments of the present disclosure will become apparent to those skilled in the art from the following detailed description, which shows and describes illustrative embodiments of the disclosure. As will be realized, the invention is capable of modifications in various aspects, all without departing from the spirit and scope of the present disclosure. Accordingly, the drawings and detailed description are to be regarded as illustrative in nature and not restrictive.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a schematic depiction of an implantable pulse generator (e.g., pacemaker, implantable cardioverter defibrillator (ICD), or etc.) electrically coupled to a patient heart via a plurality of implantable medical leads.

FIG. **2** is an isometric view of a self-expanding implantable medical stent.

FIG. **3** is plan view of a total hip arthroplasty implant for implantation in the proximal end of a patient's femur

FIGS. **4**A-**4**C, are cross sectional elevations of the substrate with the antimicrobial coating progressively being constructed thereon.

FIG. **5** is a cross sectional elevation of another embodiment of the antimicrobial coating.

FIGS. **6**A-**6**C are cross sectional elevations of the substrate with the coating progressively being constructed thereon via the successive application of polymer layers impregnated with nanoparticles.

FIGS. **7**A-**7**C are cross sectional elevations of the substrate with the coating progressively being constructed thereon via a three-step polyelectrolyte multilayer (PEM) process.

DETAILED DESCRIPTION

Implementations of the present disclosure involve implantable medical devices **10***a*, **10***b*, **10***c* and **10***d* having an antimicrobial coating **15** over an exterior substrate surface **20** of the devices, wherein the antimicrobial coating **15** includes silver nanoparticles **25***a*, **25***b* and **25***c* of various sizes. For example, the antimicrobial coating **15** may have silver nanoparticles **25***a*-**25***c* of three generally distinct sizes, the silver nanoparticles **25***a*-**25***c* serving as an antimicrobial coating **15** for the implantable medical devices **10***a*-**10***d*. The size of a nanoparticle of the coating **15** determines how fast the nanoparticle will oxidize and dissolve, perform its antimicrobial function, and be excreted from the body. The smallest nanoparticles **25***c* of the antimicrobial coating **15** will oxidize over the course of a few days following implantation of an implantable medical device employing the coating **15**, while the largest nanoparticles **25***a* will oxidize over a longer period of time. In some embodiments, the number of smallest nanoparticles **25***c* will be significantly greater than the number of large nanoparticles **25***a* or intermediate nanoparticles **25***b*.

Since most bacteria are introduced at the time of the implantation of an implantable medical device, the smallest nanoparticles **25***c* will provide most of the rigorous antimicrobial treatment during and immediately following the implantation. The bacteria that are introduced later will then be combated by the intermediate nanoparticles **25***b*, which are next to oxidize after the smallest nanoparticles **25***c*. The bacteria that are introduced the latest will be combated by the largest nanoparticles **25***a*, which are the last to oxidize. Thus, the antimicrobial coating **15** is configured to address bacteria that are introduced over an extended period.

To begin a general, non-limiting discussion regarding some of the many types of implantable medical devices that are candidates for the antimicrobial coating **15** disclosed herein, reference is made to FIG. **1**, which is a schematic depiction of an implantable pulse generator (e.g., pacemaker, implantable cardioverter defibrillator (ICD), or etc.) **10***a* electrically coupled to a patient heart **30** via a plurality of implantable medical leads **10***b*. As can be shown from FIG. **1**, the implantable pulse generator **10***a* includes a housing or can **35** in which the electronic components of the pulse generator **10***a* are hermetically sealed. The pulse generator **10***a* also includes a header **40** that receives therein the lead connector ends **45** of the respective leads **10***b* to mechanically couple the leads **10***b* to the pulse generator **10***a* and to electrically connect the electrical circuitry of the leads to the electrical circuitry of the pulse generator. In one embodiment, the pulse generator **10***a* is an implantable medical device having some or all of its exterior surfaces employing the antimicrobial coating **15** disclosed herein. For example, the exterior surfaces of the header **40** and can **35**, as well as any other exterior

surfaces of the pulse generator **10***a*, may be the substrate **20** on which the antimicrobial coating **15** is supported, as described in detail below.

In addition to the lead connector ends **45** on their respective proximal ends, each lead **10***b* may also have tip electrodes **50**, ring electrodes **55** and shock coils **60** supported on the lead tubular body **65** near the distal end of the lead **10***b*. The tip and ring electrodes may be configured to pace and/or sense, and the shock coil may be configured to administer defibrillation shocks.

In one embodiment, the implantable medical lead **10***b* is an implantable medical device having some or all its exterior surfaces employing the antimicrobial coating **15** disclosed herein. For example, any one or more or all of the exterior surfaces of the entire lead **10***b* and its components **45**, **50**, **55**, **60** and **65** may be the substrate **20** on which the antimicrobial coating **15** is supported, as described in detail below.

The antimicrobial coating **15** may be employed with other implantable medical devices. For example, as can be understood from FIG. **2**, which is an isometric view of an implantable self-expanding medical stent **10***c*, the wires or structural members **70** of the stent **10***c* may be coated with the antimicrobial coating **15** disclosed herein. Specifically, any one or more or all of the exterior surfaces of the entire stent **10***c* and its components **70** may be the substrate **20** on which the antimicrobial coating **15** is supported, as described in detail below.

The antimicrobial coating **15** may be employed with yet other implantable medical devices. For example, as can be understood from FIG. **3**, which is plan view of a total hip arthroplasty implant **10***d* for implantation in the proximal end of a patient's femur, the intra-medullary shaft **75**, neck **80** and head **85** of the hip implant **10***d* may be coated with the antimicrobial coating **15** disclosed herein. Specifically, any one or more or all of the exterior surfaces of the entire hip implant **10***d* and its components **75**, **80** and **85** may be the substrate **20** on which the antimicrobial coating **15** is supported, as described in detail below.

While the preceding examples of a medical device implant employing the antimicrobial coating **15** disclosed herein are given in the context of a pulse generator **10***a*, an implantable medical lead **10***b*, a self-expanding stent **10***c*, and a total hip arthroplasty implant **10***d*. In other embodiments, the medical device implant employing the antimicrobial coating **15** disclosed herein is any type of implant now in existence or yet to come into existence, wherein the implant is intended for implantation in a patient. Accordingly, the antimicrobial coating equipped implant disclosed herein should not be limited to the four examples given with respect to FIGS. **1-3**, but should be deemed to encompass all medical device implants with exterior surfaces capable of serving as substrates **20** for the antimicrobial coatings **15** disclosed herein.

To begin a discussion of one embodiment of the antimicrobial coating **15** employed on the exterior substrate surfaces **20** of the implantable medical devices such as those described above, reference is made to FIGS. **4A-4C**, which are cross sectional elevations of the substrate **20** with the coating **15** progressively being constructed thereon via wet deposition. As illustrated in FIG. **4**C, the antimicrobial coating **15** includes multiple layers **90**, **91**, **92** deposited in a stacked arrangement upon the substrate **20**, which is an exterior surface of an implantable medical device such as those described above with respect to FIGS. **1-3**. The innermost layer **90** (i.e., the layer extending along the outer surface of the substrate **20**) is substantially, if not entirely, formed of the largest nanoparticles **25***a*. The outermost layer **92** (i.e., the layer forming the exterior surface of the coating **15** and on the opposite side of the coating **15** from the substrate **20**) is substantially, if not entirely, formed of the smallest nanoparticles **25***c*. The middle layer **91** (i.e., the layer sandwiched between the innermost layer **90** and the outermost layer **92**) is substantially, if not entirely, formed of medium nanoparticles **25***a*.

In one embodiment of the antimicrobial coating **15** depicted in FIG. **4**C, the largest nanoparticles **25***a* are between approximately 15 nm and approximately 20 nm in diameter, the medium nanoparticles **25***b* are approximately 10 nm in diameter, and the smallest nanoparticles **25***c* are approximately 5 nm in diameter.

As can be understood from FIGS. **4A-4C**, in one embodiment, the nanoparticles **25***a*-**25***c* are coated directly onto the substrate **20** using a wet deposition method (e.g., immersion in a silver nanoparticle solution). Such an application of the layers **90-92** may be performed in several successive stages. For example, as indicated in FIG. **4**A, in a first stage, the innermost layer **90** is applied directly to the substrate **20** by dipping the substrate **20** in a solution containing the large nanoparticles **25***a* substantially or exclusively. As indicated in FIG. **4**B, in the second stage subsequent to the curing of the innermost layer **90** on the substrate **20**, the middle layer **91** is applied to the exposed outer surface of the cured innermost layer **90** by dipping the innermost layer coated substrate **20** into a solution containing the medium nanoparticles **25***b*. As illustrated in FIG. **4**C, in the third and final stage for a three layer coating **15** and subsequent to the curing of the middle layer **91** on the substrate **20**, the outermost layer **92** is applied to the exposed outer surface of the cured middle layer **91** by dipping the middle layer coated substrate **20** into a solution containing the small nanoparticles **25***c*.

In some embodiments, the coating **15** depicted in FIGS. **4A-4C** may have three layers **90-92**, more than three layers, or as few as two layers. In such embodiments, the order of dipping should be from the largest to smallest nanoparticles, resulting in an antimicrobial coating **15** wherein the smallest nanoparticles **25***c* will oxidize or elute first to treat and prevent DRIs having potentially immediate onset, the medium nanoparticles **25***b* oxidizing or eluting next to prevent DRIs that would onset later, the large nanoparticles **25***a* oxidizing or eluting last to prevent DRIs that would onset still later. In this way, the smaller nanoparticles would get eluted before the larger nanoparticles.

In one embodiment of the coating **15** of FIG. **4**C, the solution used to deposit the nanoparticles **25***a*, **25***b*, **25***c* is first comprised of water, a surfactant such as sodium saccharine, and silver nitrate. A reducing agent, such as N,N,N',N'-tetramethylethylenediamine is then added to begin the production of nanoparticles. In one embodiment, such a solution in which the substrate **20** is dipped to form the innermost layer **90** is between approximately 1% and approximately 10% by weight large silver nanoparticles **25***a* and the remainder of the solution is made of polymeric matrix such as polyurethane, polypyrrole, silicone, or etc. The solution containing the medium nanoparticles **25***b* in which the substrate **20** is dipped to form the middle layer **91** is between approximately 1% and approximately 10% by weight medium silver nanoparticles **25***b* and the remainder of the solution is made of polymeric matrix such as polyurethane, polypyrrole, silicone, or etc. The solution containing smallest nanoparticles **25***c* in which the substrate **20** is dipped to form the outermost layer **92** is between approximately 1% and approximately 10% by weight small silver nanoparticles **25***c* and the remainder of the solution is made of polymeric matrix such as polyurethane, polypyrrole, silicone, or etc.

A cross sectional elevation of another embodiment of the coating **15** is depicted in FIG. **5**. As with the previous embodi-

ment of the coating **15**, for the coating of FIG. **5**, the largest nanoparticles **25***a* are between approximately 15 nm and approximately 20 nm in diameter, the medium nanoparticles **25***b* are approximately 10 nm in diameter, and the smallest nanoparticles **25***c* are approximately 5 nm in diameter. The nanoparticles **25***a*-**25***c* are deposited directly onto the substrate **20** using a wet deposition method (e.g., immersion in a silver nanoparticle solution) employing a single solution. Specifically, all the sizes of nanoparticles **25***a*-**25***c* in the appropriate size proportions are present in solution, and the substrate **20** is dipped once into that solution. In a variation of the embodiment depicted in FIG. **5**, the substrate is dipped and allowed to cure before being dipped again in the same solution. Unlike the embodiment depicted in FIG. **4**C, wherein the sizes of nanoparticles **25***a*-**25***c* each occupy a respective layer **90**-**92** of the coating **15**, the layers **90**-**92** being arranged such that the layers **90**-**92** are located moving outwardly from large nanoparticle layer **90** to medium nanoparticle layer **91** to small nanoparticle layer **92**, the embodiment depicted in FIG. **5** has a single layer (or multiple layers where laid up via multiple dips) that includes each size of nanoparticle **25***a*-**25***c*.

In one embodiment of the coating **15** of FIG. **5**, the solution in which the substrate **20** is dipped to form the coating **15** is first comprised of water, a surfactant such as sodium saccharine, and silver nitrate. A reducing agent, such as N,N,N',N'-tetramethylethylenediamine, is then added to begin the production of nanoparticles. In one embodiment of the coating **15** of FIG. **5**, the solution in which the substrate **20** is dipped to form the coating **15** is between approximately 1% and approximately 10% by weight large silver nanoparticles **25***a*, between approximately 1% and approximately 10% by weight medium silver nanoparticles **25***b*, and between approximately 1% and approximately 10% by weight small silver nanoparticles **25***c*, the remainder of the solution being made of water, a surfactant such as sodium saccharine, and any silver nitrate that has not been reduced into nanoparticles.

To begin a discussion of another embodiment of the antimicrobial coating **15** employed on the exterior substrate surfaces **20** of the implantable medical devices such as those described above, reference is made to FIGS. **6**A-**6**C, which are cross sectional elevations of the substrate **20** with the coating **15** progressively being constructed thereon via the successive application of polymer layers **100**, **101**, **102** impregnated with nanoparticles **25**-*a*-**25***c*. As illustrated in FIG. **6**C, the antimicrobial coating **15** includes multiple polymer layers **100**, **101**, **102** deposited in a stacked arrangement upon the substrate **20**, which is an exterior surface of an implantable medical device such as those described above with respect to FIGS. **1**-**3**. The innermost polymer layer **100** (i.e., the layer extending along the outer surface of the substrate **20**) is impregnated with nanoparticles that are substantially, if not entirely, the largest nanoparticles **25***a*. The outermost polymer layer **102** (i.e., the layer forming the exterior surface of the coating **15** and on the opposite side of the coating **15** from the substrate **20**) is impregnated with nanoparticles that are substantially, if not entirely, the smallest nanoparticles **25***c*. The middle polymer layer **101** (i.e., the layer sandwiched between the innermost layer **100** and the outermost layer **102**) is impregnated substantially, if not entirely, with the medium nanoparticles **25***a*.

In one embodiment of the antimicrobial coating **15** depicted in FIG. **6**C, the largest nanoparticles **25***a* are between approximately 15 nm and approximately 20 nm in diameter, the medium nanoparticles **25***b* are approximately 10 nm in diameter, and the smallest nanoparticles **25***c* are approximately 5 nm in diameter.

Each size of nanoparticles **25***a*-**25***c* is embedded in a polymer material **105** of a respective polymer layer **100**-**102**. The multiple layers **100**-**102** are sandwiched together to form the coating **15**, which may be in the form of a coating, adhered layer, package for containing the implantable medical device, or a member or feature attached to or adjacent to the implantable medical device. The multiple layers **100**-**102** may be deposited upon the substrate **20** and each other via successive applications of layers. Depending on the embodiment, any of the various methods of embedding silver nanoparticles in polymer materials described in the following three publications can be employed: (1) Furno F, Morley K S, Wong B, Sharp B L, Arnold P L, Howdle S M, Bayston R, Brown P D, Winship P D, Reid H J. Silver nanoparticles and polymeric medical devices: a new approach to prevention of infection? *The Journal of antimicrobial chemotherapy*. December 2004; 54(6):1019-1024; (2) Stevens K N J, Croes S, Boersma R S, Stobberingh E E, van der Marel C, van der Veen F H, Knetsch M L W, Koole L H. Hydrophilic surface coatings with embedded biocidal silver nanoparticles and sodium heparin for central venous catheters. *Biomaterials*. 2011; 32(5):1264-1269; and (3) Hindi K M, Ditto A J, Panzner M J, Medvetz D A, Han D S, Hovis C E, Hilliard J K, Taylor J B, Yun Y H, Cannon C L, Youngs W J. The antimicrobial efficacy of sustained release silver-carbene complex-loaded I-tyrosine polyphosphate nanoparticles: Characterization, in vitro and in vivo studies. *Biomaterials*. 2009; 30(22):3771-3779. These three publications are incorporated by reference herein in their entireties. The methods disclosed in the three incorporated publications lead to a polymer that contains a homogenous distribution of silver nanoparticles.

As can be understood from FIGS. **6**A-**6**C, several layers **100**-**102** of polymer material **105** can be used, each layer **100**-**102** containing nanoparticles **25***a*-**25***c* of a different specific size. In one embodiment, the outermost layer **102** is biodegradable or bioabsorbable and contains the smallest nanoparticles **25***c* so that once the small nanoparticles are oxidized, the polymer material **105** would dissolve exposing the next layer **101**. This next layer **101**, which is the middle layer **101** containing the slightly larger medium nanoparticles **25***b*, is also biodegradable or bioabsorbable so that once the medium nanoparticles **25***b* are oxidized, the polymer material **105** would dissolve exposing the next layer **100**. This next layer **100**, which is the innermost layer **100**, may not be biodegradable. As a result, the largest nanoparticles **25***a*, which occupy the polymer material **105** of the innermost layer **100**, would remain for a longer period of time to provide long term antimicrobial protection.

In one embodiment of the coating of FIG. **6**C, the polymer material **105** of the outermost layer **102** and middle layer **101** is a biodegradable or bioabsorbable polymer such as one of synthetic materials poly(L-lactic acid), polycaprolactone, poly(lactide-co-glycolide), poly(ethylene-vinyl acetate), poly(hydroxybutyrate-covalerate), polydioxanone, polyorthoester, polyanhydride, poly(glycolic acid), poly(D,L-lactic acid), poly(glycolic acid-co-trimethylene carbonate), polyphosphoester, polyphosphoester urethane, poly(amino acids), cyanoacrylates, poly(trimethylene carbonate), poly (iminocarbonate), copoly(ether-esters), polyalkylene oxalates, polyphosphazenes, and polyarylates. The polymer material **105** of the outermost layer **102** and middle layer **101** can also be a natural material such as fibrin, fibrinogen, cellulose, starch, collagen, and hyaluronic acid, or etc. In one embodiment, the polymer material **105** of the innermost layer **100** is a non-biodegradable polymer such as silicone, polyamine, polystyrene, polyurethane, acrelate, polysilane, polysulfone, methoxysilane, or etc.

In one embodiment of the coating **15** of FIG. **6**C, the polymer material containing the largest nanoparticles **25***a* and therewith forming the innermost layer **100** is between approximately 1% and approximately 10% by weight large silver nanoparticles **25***a* and the remainder of the layer **100** is made of the polymer material. The polymer material containing the medium nanoparticles **25***b* and therewith forming the middle layer **101** is between approximately 1% and approximately 5% by weight medium silver nanoparticles **25***b* and the remainder of the layer **101** is made of the polymer material. The polymer material containing the smallest nanoparticles **25***c* and therewith forming the outermost layer **102** is between approximately 1% and approximately 2.5% by weight small silver nanoparticles **25***c* and the remainder of the layer **102** is made of the polymer material.

In some embodiments, the coating **15** depicted in FIGS. **6**A-**6**C may have three layers **100-102**, more than three layers, or as few as two layers. In such embodiments, the order of successive application of the layers **100-102** should be from the largest to smallest nanoparticles, resulting in an antimicrobial coating **15** wherein the smallest nanoparticles **25***c* will oxidize or elute first to treat and prevent DRIs having potentially immediate onset, the medium nanoparticles **25***b* oxidizing or eluting next to prevent DRIs that would onset later, the large nanoparticles **25***a* oxidizing or eluting last to prevent DRIs that would onset still later. In this way, the smaller nanoparticles would get eluted before the larger nanoparticles.

To begin a discussion of yet another embodiment of the antimicrobial coating **15** employed on the exterior substrate surfaces **20** of the implantable medical devices such as those described above, reference is made to FIGS. **7**A-**7**C, which are cross sectional elevations of the substrate **20** with the coating **15** progressively being constructed thereon via a three-step polyelectrolyte multilayer (PEM) process. As illustrated in FIG. **7**C, the antimicrobial coating **15** includes multiple layers **120**, **121**, **122** deposited in a stacked arrangement upon the substrate **20**, which is an exterior surface of an implantable medical device such as those described above with respect to FIGS. **1**-**3**. The innermost layer **120** (i.e., the layer extending along the outer surface of the substrate **20**) is substantially, if not entirely, formed of the largest nanoparticles **25***a*. The outermost layer **122** (i.e., the layer forming the exterior surface of the coating **15** and on the opposite side of the coating **15** from the substrate **20**) is substantially, if not entirely, formed of the smallest nanoparticles **25***c*. The middle layer **121** (i.e., the layer sandwiched between the innermost layer **120** and the outermost layer **122**) is substantially, if not entirely, formed of medium nanoparticles **25***a*.

In one embodiment of the antimicrobial coating **15** depicted in FIG. **6**C, the largest nanoparticles **25***a* are between approximately 15 nm and approximately 20 nm in diameter, the medium nanoparticles **25***b* are approximately 10 nm in diameter, and the smallest nanoparticles **25***c* are approximately 5 nm in diameter.

As can be understood from FIGS. **7**A-**7**C, the different sizes of nanoparticles **25***a*-**25***c* are assembled into polyelectrolyte multilayers (PEMs) using one of methods described in the two following publications: (1) Agarwal A, Weis T L, Schurr M J, Faith N G, Czuprynski C J, McAnulty J F, Murphy C J, Abbott N L. Surfaces modified with nanometer-thick silver-impregnated polymeric films that kill bacteria but support growth of mammalian cells. *Biomaterials. February* 2010; 31(4):680-690; and (2) Logar M, Jancar B, Suvorov D, Kostanjsek R. In situ synthesis of Ag nanoparticles in polyelectrolyte multilayers. *Nanotechnology.* 2007; 18:1-7. These two publications are incorporated by reference herein in their entireties.

These two PEM methods involve deposition of oppositely charged polyelectrolytes on substrates where the electrostatic interaction between the two components is the driving force for the multilayer buildup. Upon the absorption of a polycation onto the negatively charged substrates, the negative charges of the substrate are reversed to positive, favoring the subsequent adsorption of polyanions. This process can be repeated several times, depending on the desired number of layers and desired final structure thickness. Thus, as can be understood from FIG. **7**A-**7**C, the layers **120-122** are laid up via three successive PEM operations.

In one embodiment, polyallylamine multilayer films of silver nanoparticles can be created using the PEM method. The PEM is built by alternately dipping the substrate in a positively charged polyelectrolyte (PAH) and a negatively charged polyelectrolyte (PAA). Once the PEM is built, the substrate with the PEM is dipped into a solution of silver nitrate, deionized water, and a reducing agent such as sodium borohydride ($NaBH_4$) to begin the formation of silver nanoparticles within the PEM. The size of the particles and their distribution can be controlled by altering the PEM assembly conditions. Specifically, the average diameter of the nanoparticles increases with increasing pH of the PAA dipping solution used to build the PEM. Therefore, in creating the large nanoparticles **25***a* of the innermost layer **120**, the PEM can be built using PAA with a high pH (e.g., a pH of between approximately 3.3 and approximately 3.7) to synthesize the large nanoparticles **25***a*. In creating the medium nanoparticles **25***b* of the middle layer **121**, the PEM can be built using PAA with a medium pH (e.g., a pH of between approximately 2.8 and approximately 3.2) to synthesize the medium nanoparticles **25***b*. In creating the small nanoparticles **25***c* of the outermost layer **122**, the PEM can be built using PAA with a low pH (e.g., a pH of between approximately 2.3 and approximately 2.7) to synthesize the small nanoparticles **25***c*.

As indicated in FIG. **7**A, the first PEM layer is built on the substrate **20** using PAA with a high pH and then dipped in the silver nitrate solution to create the innermost layer **120** with its large nanoparticles **25***a*. After the innermost layer **120** has cured, the next PEM layer is built using PAA with a medium pH and then dipped in the silver nitrate solution to create the middle layer **121** with its medium nanoparticles **25***b* over the cured innermost layer **120**, as shown in FIG. **7**B. After the middle layer **121** has cured, the next PEM layer is built using PAA with a low pH and then dipped in the silver nitrate solution to create the outermost layer **122** with its small nanoparticles **25***c* over the cured middle layer **121**, as illustrated in FIG. **7**C. In some embodiments, the coating **15** depicted in FIGS. **7**A-**7**C may have three layers **120-122**, more than three layers, or as few as two layers.

In one embodiment, the PEM built with higher pH PAA produces lower concentrations of nanoparticles, and the PEM built with lower pH PAA produces higher concentrations of nanoparticles. Accordingly, by using the PEM method, in one embodiment, the innermost layer **120** may include lower concentrations of large nanoparticles **25***a*, the middle layer **121** may have higher concentrations of medium nanoparticles **25***b*, and the outermost layer **122** may have still higher concentrations of small nanoparticles **25***c*. Such an arrangement allows for larger numbers of small nanoparticles **25***c* to be released during and shortly following the implantation of the implantable medical device; followed by slower release of the

medium nanoparticles **25***b* over a later time, followed by yet slower release of the large nanoparticles **25***a* over yet a later time.

In one embodiment of the coating **15** of FIG. **7**C, the solution containing the largest nanoparticles **25***a* in which the substrate **20** is dipped to form the innermost layer **120** is between approximately 1% and approximately 10% by weight large silver nanoparticles **25***a* and the remainder of the solution is made of water, a positively charged polyelectrolyte, and a negatively charged polyelectrolyte. The solution containing the medium nanoparticles **25***b* in which the substrate **20** is dipped to form the middle layer **121** is between approximately 1% and approximately 10% by weight medium silver nanoparticles **25***b* and the remainder of the solution is made of water, a positively charged polyelectrolyte, and a negatively charged polyelectrolyte. The solution containing smallest nanoparticles **25***c* in which the substrate **20** is dipped to form the outermost layer **122** is between approximately 1% and approximately 10% by weight small silver nanoparticles **25***c* and the remainder of the solution is made of water, a positively charged polyelectrolyte, and a negatively charged polyelectrolyte

In one embodiment, the silver nanoparticles **25***a*-**25***c* of the above-disclosed embodiments are silver nanoparticles the same as, or similar to, the silver nanoparticles employed in the SilvaGard coating by AcryMed, Inc. In one embodiment, the silver nanoparticles **25***a*-**25***c* are the same as, or similar to, those disclosed in the five following publications: (1) Furno F, Morley K S, Wong B, Sharp B L, Arnold P L, Howdle S M, Bayston R, Brown P D, Winship P D, Reid H J. Silver nanoparticles and polymeric medical devices: a new approach to prevention of infection? *The Journal of antimicrobial chemotherapy*. December 2004; 54(6):1019-1024; (2) Agarwal A, Weis T L, Schurr M J, Faith N G, Czuprynski C J, McAnulty J F, Murphy C J, Abbott N L. Surfaces modified with nanometer-thick silver-impregnated polymeric films that kill bacteria but support growth of mammalian cells. *Biomaterials*. February; 31(4):680-690; (3) Flores C Y, Diaz C, Rubert A, Benitez G A, Moreno M S, Fernandez Lorenzo de Mele M A, Salvarezza R C, Schilardi P L, Vericat C. Spontaneous adsorption of silver nanoparticles on Ti/TiO2 surfaces. Antibacterial effect on *Pseudomonas aeruginosa*. *Journal of colloid and interface science*. Oct. 15 2010; 350(2):402-408; (4) Juan L, Zhimin Z, Anchun M, Lei L, Jingchao Z. Deposition of silver nanoparticles on titanium surface for antibacterial effect. *International journal of nanomedicine*. 2010; 5:261-267; and (5) Roe D, Karandikar B, Bonn-Savage N, Gibbins B, Roullet J B. Antimicrobial surface functionalization of plastic catheters by silver nanoparticles. *The Journal of antimicrobial chemotherapy*. April 2008; 61(4):869-876.

While the embodiments discussed herein with respect to FIGS. **4**A-**7**C depict three layer arrangements, in other embodiments, the number of layers may be more or less than three layers. Accordingly, the embodiments disclosed herein should not be limited to three-layer embodiments but should be considered to encompass multi-layer arrangements of more or less than three layers.

In one embodiment, the silver nanoparticles **25***a*-**25***c* are coated directly onto the substrate **20** using a sintering process. Such a process can be used to attach to titanium, plastics and other materials and is therefore applicable to a host of implantable medical devices, including both the can of an implantable pulse generator and the body of the implantable medical leads extending from the pulse generator. In one embodiment, as explained by Shlomo Magdassi, Michael Grouchko, Oleg Berezin, Alexander Kamyshny in "Triggering the Sintering of Silver Nanoparticles at Room Temperature," *ACS Nano,* 2010, 4 (4), pp 1943-1948, which is incorporated by reference herein in its entirety, electrolytes can be used to sinter nanoparticles at room temperature in electrolyte solutions such as, for example, NaCl and MgSO4.

In another embodiment, as explained by Yuhua Long, Junjie Wu, Hao Wang, Xiaoli Zhang, Ning Zhao and Jian Xu in "Rapid sintering of silver nanoparticles in an electrolyte solution at room temperature and its application to fabricate conductive silver films using polydopamine as adhesive layers," *J. Mater. Chem.,* 2011, 21, 4875-4881, which is incorporated by reference herein in its entirety, silver can be sintered at room temperature using a negatively charged poly electrolyte to trigger a spontaneous coalescence process.

As noted by Kyoung-Sik Moon, Hai Dong, Radenka Maric, Suresh Pothukuchi, Andrew Hunt, Yi Li and C. P. Wong in "Thermal behavior of silver nanoparticles for low-temperature interconnect applications," *Journal of Electronic Materials*, Volume 34, Number 2, 168-175, which incorporated by reference herein in its entirety, sintering of silver nanoparticles takes place at 150 to 300 degrees centigrade. Very small silver particles can sinter as low as 80 degrees Centigrade.

In one embodiment, as explained by Xiong Lu, Bailin Zhang, Yingbo Wang, Xianli Zhou, Jie Weng, Shuxin Qu, Bo Feng, Fumio Watari, Yonghui Ding and Yang Leng in "Nano-Ag-loaded hydroxyapatite coatings on titanium surfaces by electrochemical deposition," J. R. Soc. Interface, 2010, which incorporated by reference herein in its entirety, Nanosilver particles combined with hydroxyapatite coatings can be deposited on titanium using electrochemical deposition. Hydroxyapatite is a major component of bone and tooth enamel. Such coatings have antibacterial properties.

As can be understood from the preceding discussion, there are several methods of sintering the particles: Low temperature heating 80 to 300 degrees centigrade, chemical sintering with poly electrolytes and electrolyte solutions, electrodeposition of silver with hydroxyapatite. Also, laser beams and light have been used to sinter, AC and DC currents sinter silver ink particles, and microwaves have been used. All of the methods disclosed herein are believed to ways to sinter silver and keep it on a surface.

The foregoing merely illustrates the principles of the invention. Various modifications and alterations to the described embodiments will be apparent to those skilled in the art in view of the teachings herein. It will thus be appreciated that those skilled in the art will be able to devise numerous systems, arrangements and methods which, although not explicitly shown or described herein, embody the principles of the invention and are thus within the spirit and scope of the present invention. From the above description and drawings, it will be understood by those of ordinary skill in the art that the particular embodiments shown and described are for purposes of illustrations only and are not intended to limit the scope of the present invention. References to details of particular embodiments are not intended to limit the scope of the invention.

What is claimed is:

1. A method of applying antimicrobial protection to an implantable medical device, the method comprising;

applying an antimicrobial layer to a surface of the implantable medical device, the antimicrobial layer comprising multiple distinct sizes of silver nanoparticles;

wherein the multiple distinct sizes of silver nanoparticles comprises a first, second and third distinct sizes of silver nanoparticles, wherein the third distinct size of silver nanoparticles includes silver nanoparticles with a diameter of between approximately 1.5 times and approxi-

mately 2 times the diameter of the silver nanoparticles of the second distinct size of silver nanoparticles, the second distinct size of silver nanoparticles including silver nanoparticles with a diameter of approximately 2 times the diameter of the silver nanoparticles of the first distinct size of silver nanoparticles.

2. The method of claim **1**, wherein the first distinct size of silver nanoparticles includes silver nanoparticles with a diameter of approximately 5 nm, the second distinct size of silver nanoparticles includes silver nanoparticles with a diameter of approximately 10 nm, and the third distinct size of silver nanoparticles includes silver nanoparticles with a diameter of between approximately 15 nm and approximately 20 nm.

3. The method of claim **1**, further comprising causing the first distinct size of silver nanoparticles to be generally confined in a first sub-layer of the antimicrobial layer, the second distinct size of silver nanoparticles to be generally confined in a second sub-layer of the antimicrobial layer, and the third distinct size of silver nanoparticles to be generally confined in a third sub-layer of the antimicrobial layer.

4. The method of claim **3**, wherein the surface of the implantable medical device acts as a substrate for the antimicrobial layer, and further comprising applying the third sub-layer of the antimicrobial layer so as to adhere directly to the substrate, applying the first sub-layer to as to form an exposed outer surface of the antimicrobial layer, and applying the second sub-layer so as to be located between the first sub-layer and the third sub-layer.

5. The method of claim **4**, wherein the sub-layers are applied via a multi-step wet deposition process.

6. The method of claim **4**, wherein the sub-layers are applied via a multi-step PEM process.

7. The method of claim **1**, further comprising causing the first distinct size of silver nanoparticles to be confined in a polymer material forming at least part of a first sub-layer of the antimicrobial layer, causing the second distinct size of silver nanoparticles to be confined in a polymer material forming at least part of a second sub-layer of the antimicrobial layer, and causing the third distinct size of silver nanoparticles to be confined in a polymer material forming at least part of a third sub-layer of the antimicrobial layer.

8. The method of claim **7**, wherein the sub-layers are applied via a multi-step polymer deposition process.

9. The method of claim **7**, wherein the sub-layers are applied via a multi-step sintering process.

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